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(54) Title: ANTIMICROBIAL SITE DRESSINGS

(57) Abstract: ANTIMICROBIAL SITE DRESSING ABSTRACT The present invention comprises antimicrobial articles for use with a percutaneous device, comprising a matrix which may contact the percutaneous device in a three-dimensional mode and release antimicrobial agents (e.g., silver ions) to the percutaneous device access site. In addition, the antimicrobial article of the present invention may donate moisture to a dry dermal site (e.g., a dry wound bed) and/or absorb liquid or exudates of a dermal site. The present invention also comprises methods for treating and/or preventing an infection using the antimicrobial articles of the present invention.

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ANTIMICROBIAL SITE DRESSINGS

RELATED APPLICATIONS

This application claims the priority of U.S. Provisional Patent Application No. 60/796,039, filed April 28, 2006, which is herein incorporated in its entirety.

FIELD OF THE INVENTION

The present invention relates to antimicrobial articles for the protection of percutaneous device access sites and methods of use the same.

BACKGROUND OF THE INVENTION

According to the United States Centers for Disease Control and Prevention (CDC), an estimated 250,000 cases of bloodstream infections associated with central venous catheters occur each year in U.S. hospitals. These infections add approximately $25,000 in patient care costs per episode. In addition, the mortality associated with these infections is 18% or 45,000 deaths per years in the United States, see, CDC, Guidelines for the Prevention of Intravascular Catheter-Related Infections, Recommendations and Reports, Morbidity and Mortality Weekly Report, August 9, 2002, Vol. 51, No. RR-10.

Various antimicrobial dressings have been used to prevent and/or reduce infections related to the uses of percutaneous devices. For example, BioPatch® Dressing from Johnson and Johnson is reported to reduce the incidence of catheter-related bloodstream infection by 60% and local infection by 44%. This polyurethane foam with chlorhexidine gluconate (CHG) may be used together with vascular percutaneous devices such as central venous catheters, arterial catheters, and PICC lines, as well as non-vascular percutaneous devices, such as orthopedic pins, epidural catheters, and drain tubes. It may continuously deliver the antimicrobial CHG for up to seven days and absorb up to eight times its weight in fluid. In addition, Acticoat 7 (with SILCRYST™ Nanocrystals) Antimicrobial Barrier Dressing provides an effective barrier to bacterial penetration, which may help reduce infection in partial and full thickness wounds. It contains a nanocrystalline coating of pure silver for delivering antimicrobial barrier activity to a dermal site, a rayon/polyester core for

managing moisture level and controlling silver release, and a silver-coated high-density polyethylene mesh for facilitating the passage of silver through the dressing. It is reported that in vitro tests indicated that the Acticoat 7 dressing may be effective against more than 150 pathogens, such as, resistant strains of bacteria (e.g., antibiotic-resistant strains of Pseudomonas, methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE)) and fungi.

Nonetheless, a number of factors limited the applications and/or the efficacies of the existing products. For example, it is well known that CHG can cause hypersensitivity reactions and has not been proven safe for pediatric applications. In addition, too much silver ions released from a dressing may cause dermal discoloration and may also be cytotoxic. Another drawback of the dressings currently known in the art is that these dressings have only point or two-dimensional contacts with a percutaneous device, leaving gaps between the dressing and the device and exposing the percutaneous device access site to potential pathogen attacks.

Therefore, there exists a need for an antimicrobial article for use with a percutaneous device having features, such as, providing a minimized or reduced gap between the article and the percutaneous device for reducing, minimizing, or eliminating infections related to the use of such percutaneous device, providing a sustained release of antimicrobial agents, facilitating the maintenance of optimal moisture balance, and/or being non- or less toxic, non- or less irritating, non- or less staining, and/or non- or less sensitizing.

SUMMARY OF THE INVENTION

The present invention provides an article of manufacture for use with a percutaneous device, comprising a matrix, wherein the matrix comprises a first passage, a second passage, and an antimicrobial agent, wherein the first passage connects to the second passage, and wherein the matrix contacts a percutaneous device in a three-dimensional mode. In one embodiment, a first passage may extend from an edge of the matrix toward an internal point of the article. In another embodiment, a second passage may connect with the first passage at one end of the first passage. In yet another embodiment, at least a portion of a second passage comprises a curved shape. In still another embodiment, the antimicrobial agent may be a silver-containing antimicrobial agent, such as, without limitation, a silver

compound or a metallic silver (e.g., a silver nanoparticle). The silver containing antimicrobial agent may be released when the antimicrobial article is applied. In addition, the antimicrobial article of the present invention may donate moisture to a dry dermal site (e.g., a dry wound bed) and/or absorb liquid or exudates of a dermal site.

The present invention also provides a method of treating or preventing an infection comprising contacting a percutaneous device and the percutaneous device access site with the antimicrobial article of the present invention.

Other features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating the preferred embodiments of the present invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the present invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF FIGURES

Figure 1 shows a representative antimicrobial article produced in accordance with one embodiment of the present invention.

Figure 2 shows representative schematic diagrams of interactions between a percutaneous device and a dressing known in the art and between such a device and the antimicrobial article produced in accordance with one embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural references, unless the content clearly dictates otherwise. Thus, for example, reference to "an antimicrobial agent" includes a plurality of such antimicrobial agents and equivalents thereof known to those skilled in the art, and reference to "the matrix" is a reference to one or more such matrices and equivalents thereof known to those skilled in the art, and so forth. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The present invention generally relates to novel articles and methods for controlling bioburden and managing moisture level at, around, or adjacent to a percutaneous device assess site. The article of the present invention may have at least one of the features, such as, providing a minimized or reduced gap between the article and the percutaneous device for reducing, minimizing, or eliminating infections related to the use of such percutaneous device, providing a sustained release of antimicrobial agents, facilitating the maintenance of optimal moisture balance, and/or being non- or less toxic, non- or less irritating, non- or less staining, and/or non- or less sensitizing. For example, the present invention provides articles which may provide broad spectrum antimicrobial agents to a percutaneous device assess site which may prevent MSRA and VRE infection for up to seven days. It may also provide moisture to a dry percutaneous device assess site and/or absorb more than about five times its weight in exudates from the percutaneous device access site.

The term "percutaneous device," as used herein, includes any devices which administer, remove, absorb, and/or release a substance, or access and/or monitor, by way of, or effect through, the skin. For example, a percutaneous device may be a medical device which accesses inner organs or other tissue via needle-puncture or other methods of transit of the skin. It may also be a medical device which effect through an "opened" skin, where, for instance, the skin was opened using a medical device, such as, a scalpel, followed by the administration of the percutaneous device and then the closing of the opening. Examples of percutaneous devices include, without limitation, a vascular device (such as, an intravenous catheter, a central venous line, an arterial catheter, a peripheral catheter, or a dialysis catheter), or a non-vascular device (such as, an external fixator pin, a peritoneal dialysis catheter, an epidural catheter, a chest tube, or a gastronomy feeding tube).

In one aspect, the present invention provides an article of manufacture for use with a percutaneous device, comprising a matrix, wherein the matrix comprises a first passage, a second passage, and an antimicrobial agent, wherein the first passage connects to the second passage, and wherein the matrix may contact a percutaneous device in a three-dimensional mode. Figure 1 illustrates a representative example of the article produced in accordance with one embodiment of the present invention, which comprises a matrix **10**, a first passage [the slit **20**], a second passage [the slit **30**], and silver-based antimicrobial agents.

The matrix may be in any shape suitable for the purposes of the application and may be fabricated using any suitable materials known in the art. In one embodiment, the matrix may be in the shape of a disc. In another embodiment, the matrix may contain a biocompatible material. For example, the matrix may contain a plurality of layers and at least the layer which has access to a dermal site may be made using a biocompatible material. In yet another embodiment, the matrix may contain a swellable material which may confer certain desirable features to the article of the present invention, such as, to allow it to absorb wound exudates. Examples of materials for producing the matrix of the present invention may include, without limitation, those taught in U.S. Patent Nos. 7,160,553; 6,897,349; 6,605,751; 6,355,858; 5,928,174; 5,833,665; and 5,196,190, and U.S. Patent Application Publication Nos. 2007/0003603; 2005/0226931, 2001/0041188; and U.S. Patent Application Serial Nos. 11/572,899; 11/663.236; and 11/704,167. All of which are hereby incorporated in their entirety.

An aspect of the present invention, the active agent, which may be a heavy metal ion, such as silver, is incorporated into the matrices so that the agent is released directly from the matrices and delivered to the contact substrate such as the dermal site or the percutaneous device. The incorporated active agents may be released over a period of time, and in this way, the articles of the present invention retain their ability to kill or inhibit microorganisms over an extended period of time. As used herein, the term silver includes all silver salts or silver compounds, including, but not limited to, silver chloride, silver phosphate, silver sulfate, silver iodide or silver bromide. The active form of the silver salt is the silver ion, as is the case for the active forms of the heavy metals.

In one embodiment, the matrix of the present invention may comprise a hydrophilic matrix material, which may be flexible and elastic, and may be permeable to substances such as inorganic salts, aqueous fluids, and dissolved gaseous agents including oxygen. The hydrophilic matrix material may be a natural, synthetic, or semi-synthetic polymer. Examples of the polymers that may be used for the construction of the antimicrobial article include, but are not limited to, collagen, animal hide, hyaluronic acid, dextran, alginate, hydrophilic fibers of cross-linked and/or non-cross-linked celluloses (such as carboxymethy cellulose and hydroxymethyl cellulose), cotton, rayon, fibers made from polyacrylates, fibers of

calcium alginates, polyacrylamide, polyvinyl's (PVP, and PVC), polyacrylate, polybuterate, polyurethane foam, silicone elastomer, rubber, nylon, vinyl, and cross linked dextran. For instance, the matrix of the present invention may comprise polymerized chains of acrylamide monomer, wherein the acrylamide monomers may be cross-linked with a cross-linking agent (e.g., methylenebisacrylamide, bisacrylylycystamine, or diallyltartar diamide). In embodiments where cross-linked dextran is used, the molecular weight of the dextran polymer may be between about 50,000 and about 500,000. Methods for making matrices using these polymers (e.g. polyacrylamide polymer) are well known in the art.

The matrix of the present invention may be moist or dry, which may facilitate the management of moisture balance at or near a percutaneous device access site. In one embodiment, the matrix may comprise water, such as, about 10-40% of water or about 20% water, which may provide moisture to a dry dermal site. In another embodiment, the matrix may absorb liquid, such as, exudates from a percutaneous device access site. For example, the matrix may absorb up to about five times its weight in liquid, such as, exudates from a percutaneous device access site.

In addition, the matrix of the present invention may be translucent, semi-transparent, or transparent, which may allow for visualization and monitoring the percutaneous device access site.

An example of a matrix of the present invention comprises a natural or synthetic polymer and a non-gellable polysaccharide. Natural hydrophilic polymers that may be used include, but are not limited to collagen, animal hide, hyaluronic acid, dextran and alginate. Additionally included are hydrophilic fibers of cross-linked and non-cross-linked celluloses such as carboxymethyl cellulose and hydroxymethyl cellulose; cotton, rayon, and of fibers made from polyacrylates; and fibers of calcium alginates that may be used. Synthetic polymers that may be used include, but are not limited to polyacrylamide, polyvinyl's (PVP, and PVC), polyacrylate, polybuterate, polyurethane foam, silicone elastomer, rubber, nylon, vinyl or cross linked dextran. If cross-linked dextran is used, it is preferred that the molecular weight of the dextran polymer is between 50,000 and 500,000. Non-gellable polysaccharide may include a non-gellable galactomannan macromolecule such a guar gum. A range of guar gum between approximately 0.01 kg to 100 kg, between approximately 0.1 kg to 10 kg, or between approximately 0.5 kg to 2 kg is generally sufficient. Other non-gellable

polysaccharides may include lucerne, fenugreek, honey locust bean gum, white clover bean gum and carob locust bean gum.

Should it be desired to decrease the permeability of the articles of the present invention, water loss control agents may be applied to one or more surfaces of the device. Water loss control agents are known in the art and include, but are not limited to, petrolatum, glycolipids, ceramides, free fatty acids, cholesterol, triglycerides, sterylesters, cholesteryl sulfate, linoleic ethyl ester and silicone oil.

If desired, a plasticizer may also be added to the matrix material. Plasticizers are known in the art. An example of a plasticizer is glycerol and water, however, propylene glycol and butanol may also be used. If glycerol is used, a range of between approximately 0.5 kg to 50 kg, between 1 kg and 30 kg, or between approximately 5 kg to 15 kg is generally sufficient. The plasticizer may be added in the initial mixture of polymer and cross-linking agent.

If desired, a hydration control agent may be incorporated into the matrix. A hydration control agent that may be used is an isopropyl alcohol, however, ethanol, glycerol, butanol, and propylene glycol may also be used. A range of isopropyl alcohol of between approximately 0.1 kg to 10 kg, between approximately 0.2 kg to 5 kg and between approximately 0.5 kg to 2 kg is generally sufficient.

An embodiment of a matrix of the present invention may comprise polymerized chains of acrylamide monomer, wherein the acrylamide monomers are cross-linked with a cross-linking agent, a non-gellable polysaccharide, and an active agent or pharmaceutical directly incorporated into the matrix. The active agent, such as a silver-containing compound, may be added during the formation of the matrix or after matrix formation. A range of acrylamide between approximately 1 kg to 100 kg, between approximately 2 to 50 kg, or between approximately 5 kg to 20 kg is generally sufficient. An example of a matrix comprising cross-linked polyacrylamide and guar gum is disclosed in U.S. Pat. No. 5,196,160 to Nangia.

A cross-linking agent is NNNN'-methylenebisacrylamide, andother appropriate cross-linking agents such as bisacrylylycystamine and diallyltartar diamide may also be used. If NNNN'-methylenebisacrylamide is used, a range of between approximately 0.01 kg to 1 kg, between approximately 0.02 kg to 0.5 kg, or between approximately 0.05 kg to 0.3 kg is generally sufficient. As noted above, non-

gellable polysaccharide include a non-gellable galactomannan macromolecule such a guar gum, but other non-gellable polysaccharides may include lucerne, fenugreek, honey locust bean gum, white clover bean gum and carob locust bean gum.

Ammonium persulfate and TEMED (N,N,N'N'-tetramethylethylene diamine) may also be added to the matrix. A range of ammonium persulfate between approximately 0.01 kg to 1 kg, between approximately 0.02 kg to 0.5 kg, or between approximately 0.05 kg to 0.2 kg is generally sufficient. Additionally, a range of TEMED between approximately 0.01 kg to 1 kg, between approximately 0.02 kg and 0.5 kg, or between approximately 0.05 kg to 0.3 kg is generally sufficient.

The matrix of the present invention may further comprise various additives as well as other active or inactive agents and/or components, such as, without limitation, a water loss control agent (e.g., petrolatum, glycolipids, ceramides, free fatty acids, cholesterol, triglycerides, sterylesters, cholesteryl sulfate, linoleic ethyl ester, or silicone oil), a plasticizer (e.g., glycerol, propylene glycol, and butanol), a hydration control agent (e.g., isopropyl alcohol, ethanol, glycerol, butanol, and propylene glycol). In one embodiment, the matrix of the present invention may comprise a non-gellable polysaccharide, such as, without limitation, a non-gellable galactomannan macromolecule (e.g., a guar gum), lucerne, fenugreek, honey locust bean gum, white clover bean gum, and carob locust bean gum. The term "active agent" as used herein may include, without limitation, antimicrobial agents, gases, mycoplasma treatments, growth factors, proteins, nucleic acids, angiogenic factors, anesthetics, mucopolysaccharides, metals, pharmaceuticals, chemotherapeutic agents, herbicides, growth inhibitors, growth promoters, wound healing agents, indicators of change in the environment, enzymes, nutrients, vitamins, minerals, carbohydrates, fats, fatty acids, nucleosides, nucleotides, amino acids, sera, antibodies and fragments thereof, lectins, immune stimulants, immune suppressors, coagulation factors, neurochemicals, cellular receptors, antigens, adjuvants, radioactive materials, and combinations thereof. In one embodiment, the matrix of the present invention may comprise a plurality of growth factor agents, which include, without limitation, basic fibroblast growth factor (bFGF), acidic fibroblast growth factor (aFGF), nerve growth factor (NGF), epidermal growth factor (EGF), insulin-like growth factors 1 and 2, (IGF-1 and IGF-2), platelet derived growth factor (PDGF), tumor angiogenesis factor (TAF), vascular endothelial growth factor (VEGF), corticotropin releasing factor (CRF),

transforming growth factors α and β (TGF-α and TGF-β), granulocyte-macrophage colony stimulating factor (GM-CSF), the interleukins (e.g., interleukin-8), and the interferons.

In another embodiment, the matrix of the present invention may comprise proteins that may be useful in the treatment of wounds include, without limitation, collagen, cross-linked collagen, fibronectin, laminin, elastin, and cross-linked elastin, or combinations and fragments thereof. In yet another embodiment, the matrix of the present invention may comprise acid mucopolysaccharides including, without limitation, heparin, heparin sulfate, heparinoids, dermatan sulfate, pentosan polysulfate, chondroitin sulfate, hyaluronic acid, cellulose, agarose, chitin, dextran, carrageenin, linoleic acid, and allantoin. In addition, adjuvants or compositions that boost an immune response, as well as antibodies or antibody fragments, may also be used in conjunction with the antimicrobial article of the present invention.

The article of the present invention may contain a plurality of passages, or slits. The passages of the present invention may be in any suitable shape or form, such as, without limitation, a linear form, a curved formed, an irregular form, or combinations thereof. In one embodiment, the first passage may be a slit which may extend from an edge of the matrix, for example, as illustrated in Figure 1 (Slit **20**). In another embodiment, the second passage may comprise a curved shape. The second passage may connect with the first passage at any suitable point/location on the second passage. For example, the first slit **20** may connect with the second slit **30** at the middle of the second slit **30**, as illustrated in Figure 1.

Unlike the devices unknown in the art, the article of the present invention may contact a percutaneous device in a three-dimensional mode, for example, without limitation, as illustrated in Figure 2. Conventional dressings associate with a percutaneous device through a point contact or through a two-dimensional contact, i.e., all the contacts between the dressings and the percutaneous device are planar contracts which occur on the same plane, see, e.g., Figure 2. The association of a conventional dressing and a percutaneous device in such modes leaves considerable gaps between the conventional dressing and the percutaneous device, as well as leaves the percutaneous device and the percutaneous device assess site available for exposure to various pathogens. In comparison, the three-dimensional interaction between the article of the present invention and a percutaneous device substantially

reduces, minimizes, or eliminates the gap between these devices while simultaneously reducing, minimizing, or eliminating the exposure of the percutaneous device access site to various pathogens, see, e.g., Figure 2.

The article of the present invention may contain at least one antimicrobial agent. The term "antimicrobial agent" as used herein includes a substance, such as a compound or an ion, that is capable of destroying or inhibiting the growth and/or proliferation of a microorganism, such as, an anti-bacterial agent, an anti-fungal agent, an anti-viral agent, and/or an anti-parasitic agent. An antimicrobial agent may be a composition produced by or derived from certain bacteria, fungi, plants, and other organisms, and derivatives and variants thereof. An antimicrobial agent may also be synthesized or semi-synthesized chemically. In one embodiment, an antimicrobial agent may be a salt, a small molecule organic compound, a lipid, a carbohydrate, a polypeptide, a nucleic acid, or combinations thereof. Examples of antimicrobial agents include, without limitation, acyclovir, amphotericin B, ampicillin, atovaquone, azithromycin, bacitracin, carbomycin, cephalosporin, chloramphenicol, chlorotetracyclin, ciprofloxacin, clarithromycin, clindamycin, clofazimine, cycloheximide, dapsone, diclazaril, doxycycline, erythromycin, ethambutol, fluconazole, fluoroquinolones, foscarnet, fumigillin, ganciclovir, gentamicin, griseofulvin, iatroconazole, kanamycin, ketoconazole, lincomycin, methicillin, miconazole, neomycin, ofloxacin, oleandomycin, paromomycin, penicillin, pentamidine, polymyxin-B, pyrazinamide, pyrimethamine, rifabutin, rifampicin, rifamycin, sparfloxacin, streptomycin, sulfadiazine, tetracycline, trifluorouridine, vancomycin, and Zn-pyrithione, as well as heavy metals including, without limitation, copper, gold, platinum, silver, and zinc, and combinations thereof including, e.g., salts, such as chloride, bromide, iodide, and periodate, and complexes with carriers, and other forms.

In one embodiment, the antimicrobial agent may be a silver-containing antimicrobial agent, such as, without limitation, a silver-containing compound or complex, or a silver nanoparticle. Various silver-containing antimicrobial agents suitable for the purposes of the present invention are known in the art, such as, those disclosed in U.S. Patent Nos. 7,160,553; 6,897,349; 6,605,751; 6,355,858; 5,928,174; 5,833,665; and 5,196,190, and U.S. Patent Application Publication Nos. 2007/0003603; 2005/0226931, 2001/0041188; and U.S. Patent Application Serial

Nos. 11/572,899; 11/663.236; and 11/704,167. All of which are incorporated in their entireties.

The release of an antimicrobial agent, e.g., a silver-based antimicrobial agent, may be a sustained or controlled release. Methods for formulating a sustained/controlled release composition for medical applications are well known in the art. For example, the article of the present invention may comprise a water-containing, polyacrylate hydrophilic matrix and silver nanoparticles as the antimicrobial agents. Such a matrix has been shown to be capable of releasing silver ions in a sustained mode over an extended period of time, such as, up to seven days. In various embodiments of the present invention, the release of silver ions to a percutaneous device access site may be influenced by the release of exudates from the percutaneous device access site, wherein the exposure to wound moisture dissolves the silver reservoir and stimulates the release of silver ions into the wound site. The sustained release of silver means fewer dressing changes, which may result in less exposure of the percutaneous access site to the environment, and thus, reduce the risk of infection and lower hospital costs.

In another aspect, the present invention provides a method of treating or preventing an infection, comprising contacting a percutaneous device and a percutaneous device access site with the antimicrobial article of the present invention. The infection may be any infection caused by a microbial pathogen, such as, a bacterium, a fungus, a virus, and/or a parasite.

Whereas this invention has been described in detail with particular reference to preferred embodiments, it is understood that variations and modifications can be effected within the spirit and scope of the invention, as described herein before and as defined in the appended claims. The corresponding structures, materials, acts, and equivalents of all means plus function elements, if any, in the claims below are intended to include any structure, material, or acts for performing the functions in combination with other claimed elements as specifically claimed.

EXAMPLE 1 Light Stable Silver Salt Matrix

It has been found that silver salts such as silver chloride are generally stable in the salt form. Moreover, many silver salts such as silver phosphate and silver sulfate are only weakly soluble in aqueous solvent. Methods of the present invention comprise preparing a salt of silver during the preparation of the matrix, and preferably the matrix is a hydratable polyacrylate polymer.

The formation of the weakly soluble salt, silver chloride, is fully dispersed throughout the matrix and provide the precursor for the formation of the sustained release silver. The deposition of collodial silver chloride or other weakly soluble salt throughout the matrix is accomplished by any one of several methods of the present invention. In one method, the pre-formed salt, such as silver chloride, was incorporated along with other components during the compounding of the matrix formulation prior to polymerization. Another method comprises sequentially adsorbing or absorbing solutions comprising the precursor components, such as weakly soluble salts into a matrix. For example, a solution containing chloride ions was added to a polymerized hydrophilic matrix, where the solution was adsorbed or absorbed by the matrix. A second solution, containing silver ions, was added to the matrix to form a colloid of silver chloride in the matrix. Another method, is the sequential addition of anions and cations, in no particular order, during the compounding of the material mixture, causing the formation and dispersion of the colloid in the mixture prior to polymerization.

Chloride ions comprise any dissociable salt, including, but not limited to, sodium chloride, potassium chloride, copper chloride, ferric chloride, zinc chloride calcium chloride and hydrochloric acid. Such chloride ions may be added in solution or dry form.

An ionic silver solution comprises compositions such as those prepared by dissolving a salt of silver, including but not limited to silver nitrate, silver acetate, silver citrate, and silver sulphate, into water. The silver ions may also be added in a dry form.

When the polymer was catalyzed to gel, the finely dispersed silver chloride was immobilized within the polymer. Since AgCl is only weakly soluble in aqueous solutions the re-association to AgCl is strongly favored. However the ionic form is unstable and may react to light to form insoluble elemental silver (Ag_o). This form has

minimal antimicrobial activity and moreover is a black precipitate that strongly discolors the matrix when it is formed. In addition the ionic form (Ag^+) is highly reactive with functional electron donating groups which may reduce its antimicrobial effect. Therefore it is desirable to stabilize the silver by providing an excess of chloride ions in the matrix.

A matrix comprising a polyacrylate hydratable matrix produced according to U.S. Pat. No. 5,196,190 and containing silver was made using the following steps. The silver containing polyacrylate matrix was made by mixing 185 g acrylamide and 2 g bisacrylamide into 3330 g of water containing between 33.3 g of sodium chloride. To this mixture, was added 21 g of guar gum and 188 g of glycerol. After mixing to homogeneity, a solution containing 0.563 g silver nitrate was slowly added to the mixing batch. The polymerization of the mixture was accomplished by blending 1.8 ml TEMED and 2.6 g ammonium persulphate into the mixture. The mixture was poured into the appropriate molds before polymerization in a dark place. The gelled polymer was removed from the mold, dehydrated by mild heat in a darkened drier and then rehydrated by humidification to a desired moisture content, 22% w/w. The matrix was then cut to form the article with one or two passages for use with percutaneous devices.

EXAMPLE 2

The present invention also comprises compositions and devices comprising preformed hydrophillic fiber matrices and methods for making and using such materials with antimicrobial activity. Pre-formed cross-linked hydrophilic fibers are readily available through commercial channels for on-processing, packaging and sterilization for use in wound and other medical applications. Incorporation of silver into fibrous materials by an impregnation method that causes the in situ formation of a stabilized silver colloid complex within and around the fibrous material was used to make matrices for the present invention.

One method of making materials with antimicrobial activity was to disperse a chloride salt of sodium or copper or iron in water at a concentration that remains in solution when the water was combined with an alcohol solvent, including, but not limited to, isopropyl alcohol and ethanol. The fibrous matrix materials for impregnation were then immersed in a bath of the chloride ions so that the material is

completely immersed. After a suitable time the material was then removed and blotted of excess chloride-containing solvent. Then the material was immersed in a similar aqueous/alcohol bath that contains silver and copper or iron ions. After a suitable time, the material is removed, blotted of excess reagent and air dried. It is desirable that the ratio of water to alcohol in mixtures that contain the ionic elements not exceed a concentration that would cause hydrophilic materials to begin to gel. A range comprises 5-15% aqueous, and it is suggested that the aqueous portion not be greater than 50%. Reversal of the immersion sequence is inconsequential to the success of impregnation of the fibrous materials.

Hydrophilic fibrous polymer materials such as cross-linked carboxymethyl cellulose, calcium alginates and textiles such as cotton comprising silver-containing compounds provide matrices for the present invention. These hydrophilic materials aggressively absorb aqueous solutions which often cause gelling of the matrix materials. Gelled materials may be subsequently dehydrated, but seldom retain their original properties after absorption of water. Therefore it is impractical to use a substantially aqueous vehicle for the delivery of ionic silver and chloride into the matrix material where nucleation in situ of colloid would be expected to occur. This excludes the method of precipitating AgCl in situ using water as solvent. These hydrophilic polymers do not absorb alcohol, therefore a AgCl precipitation in a water:alcohol solution to partially hydrate fibers with reagents was performed.

A. This experiment showed the use of either acetone, isopropyl alcohol or ethanol as the solvent phase of an aqueous:alcohol bath for impregnation of silver into cross-linked carboxymethyl cellulose.

The following combinations of reagents were produced and tested for efficacy in allowing nucleation of AgCl in the solvent phase. 1) Add 0.177 g NaCl to 3.333 mL H_2O. 2) Add 90 g Acetone, IPA, or EtOH. Add 6.666 mL $AgNO_3$ sol (0.11325 g/50 ml H_2O) It was concluded that the ethanol was the preferred alcohol for the delivery vehicle.

The nucleation of silver chloride colloid in the hydrophilic polymer was accomplished by preparing an aqueous:alcohol solution of sodium chloride in which various hydrophilic materials were immersed. After an appropriate time an aqueous:alcohol solution containing silver nitrate was added. The materials were then removed, blotted of excess materials and air dried. They were then tested for antimicrobial activity against Staph. aureus by zone inhibition assay, for skin staining properties and for discoloration in light. 1) Added 0.1777 g NaCl to 2 ml H_2O2) Added 0.006795 g $AgNO_3$ to 100 µl H_2O 3) Added 25

g EtOH to NaCl and $AgNO_3$ solutions 4) Place a 2x2 inch square of Tegagen, Algisite M, Aquacel, or Algisite Rope into the NaCl solutions. 5) After a few seconds, add the $AgNO_3$ solution. 6) After a few seconds, remove dressings and blot dry. 7) Test for sustained release on staph zone inhibition plates, for skin staining, expose to light.

Silver was incorporated into hydrophilic fibers in amounts that allowed for sustained release. IPA or acetone may be used with more soluble chloride salts ($CuCl_2$, $FeCl_3$) but ethanol was used with sodium chloride. The resulting materials possessed antimicrobial activity and do not appreciably discolor in the presence of light.

CLAIMS

What is claimed is:

1. An article of manufacture for use with a percutaneous device, comprising a matrix, wherein the matrix comprises a first passage, a second passage, and an antimicrobial agent, wherein the first passage connects to the second passage, and wherein the matrix contacts a percutaneous device in a three-dimensional mode.

2. The article of Claim 1, wherein the antimicrobial agent is a silver containing compound.

3. The article of Claim 1, further comprising at least one active agent.

4. The article of claim 3, wherein the active agent is an antimicrobial agent, antifungal agent, antibacterial agent, anti-viral agents, antiparasitic agent, anaesthetic, mucopolysaccharide, growth factor, protein, angiogenic factor, wound healing agent or adjuvant, or combinations thereof.

5. The article of claim 4, wherein the antimicrobial agent is isoniazid, ethambutol, pyrazinamide, streptomycin, clofazimine, rifabutin, fluoroquinolones, ofloxacin, sparfloxacin, rifampin, azithromycin, clarithromycin, dapsone, tetracycline, erythromycin, ciprofloxacin, doxycycline, ampicillin, amphotericin B, ketoconazole, fluconazole, pyrimethamine, sulfadiazine, clindamycin, lincomycin, pentamidine, atovaquone, paromomycin, diclazaril, acyclovir, trifluorouridine, foscarnet, penicillin, gentamicin, ganciclovir, iatroconazole, miconazole, Zn-pyrithione, silver salts of chloride, bromide, iodide or periodate.

6. The article of c Claim 4, wherein the growth factor is basic fibroblast growth factor, acidic fibroblast growth factor, nerve growth factor, epidermal growth factor, insulin-like growth factors 1 and 2, platelet derived growth factor, tumor angiogenesis factor, vascular endothelial growth factor, corticotropin releasing factor, transforming

growth factors .alpha. and .beta., interleukin-8, granulocyte-macrophage colony stimulating factor, interleukins, or interferons.

7. The article of Claim 4, wherein the mucopolysaccharide is heparin, heparin sulfate, heparinoids, dermatan sulfate, pentosan polysulfate, chondroitin sulfate, hyaluronic acid, cellulose, agarose, chitin, dextran, carrageenin, linoleic acid, or allantoin.

8. The method of Claim 4, wherein the protein is collagen, cross-linked collagen, fibronectin, laminin, elastin, cross-linked elastin, antibodies, or combinations or fragments thereof.

9. The article of Claim 1, wherein the matrix is made from a natural or synthetic hydrophilic polymer.

10. The article of Claim 9, wherein the polymer is collagen, animal hide, hyaluronic acid, dextran, alginate, hydrophilic fibers of cross-linked and/or non-cross-linked celluloses, carboxymethy cellulose, hydroxymethyl cellulose, cotton, rayon, fibers made from polyacrylates, fibers of calcium alginates, polyacrylamide, polyvinyls, PVP, PVC, polyacrylate, polybuterate, polyurethane foam, silicone elastomer, rubber, nylon, vinyl, and cross linked dextran.

11. A method of treating or preventing an infection, comprising contacting a percutaneous device and a percutaneous device access site with an antimicrobial article, wherein the article comprises a matrix, wherein the matrix comprises a first passage, a second passage, and an antimicrobial agent, wherein the first passage connects to the second passage, and wherein the antimicrobial article contacts the percutaneous device in a three-dimensional mode.

12. The method of Claim 11, wherein the antimicrobial agent is a silver containing compound.

13. The method of Claim 11, further comprising at least one active agent in the matrix.

14. The method of Claim 13, wherein the active agent is an antimicrobial agent, antifungal agent, antibacterial agent, anti-viral agent, antiparasitic agent, anaesthetic, mucopolysaccharide, growth factor, protein, angiogenic factor, wound healing agent or adjuvant, or combinations thereof.

15. The method of Claim 14, wherein the antimicrobial agent is isoniazid, ethambutol, pyrazinamide, streptomycin, clofazimine, rifabutin, fluoroquinolones, ofloxacin, sparfloxacin, rifampin, azithromycin, clarithromycin, dapsone, tetracycline, erythromycin, ciprofloxacin, doxycycline, ampicillin, amphotericin B, ketoconazole, fluconazole, pyrimethamine, sulfadiazine, clindamycin, lincomycin, pentamidine, atovaquone, paromomycin, diclazaril, acyclovir, trifluorouridine, foscarnet, penicillin, gentamicin, ganciclovir, iatroconazole, miconazole, Zn-pyrithione, silver salts of chloride, bromide, iodide or periodate.

16. The method of Claim 14, wherein the growth factor is basic fibroblast growth factor, acidic fibroblast growth factor, nerve growth factor, epidermal growth factor, insulin-like growth factors 1 and 2, platelet derived growth factor, tumor angiogenesis factor, vascular endothelial growth factor, corticotropin releasing factor, transforming growth factors .alpha. and .beta., interleukin-8, granulocyte-macrophage colony stimulating factor, interleukins, or interferons.

17. The article of Claim 14, wherein the mucopolysaccharide is heparin, heparin sulfate, heparinoids, dermatan sulfate, pentosan polysulfate, chondroitin sulfate, hyaluronic acid, cellulose, agarose, chitin, dextran, carrageenin, linoleic acid, or allantoin.

18. The method of Claim 14, wherein the protein is collagen, cross-linked collagen, fibronectin, laminin, elastin, cross-linked elastin, antibodies, or combinations or fragments thereof.

19. The article of Claim 11, wherein the matrix is made from a natural or synthetic hydrophilic polymer.

20. The article of Claim 19, wherein the polymer is collagen, animal hide, hyaluronic acid, dextran, alginate, hydrophilic fibers of cross-linked and/or non-cross-linked celluloses, carboxymethy cellulose, hydroxymethyl cellulose, cotton, rayon, fibers made from polyacrylates, fibers of calcium alginates, polyacrylamide, polyvinyls, PVP, PVC, polyacrylate, polybuterate, polyurethane foam, silicone elastomer, rubber, nylon, vinyl, and cross linked dextran.

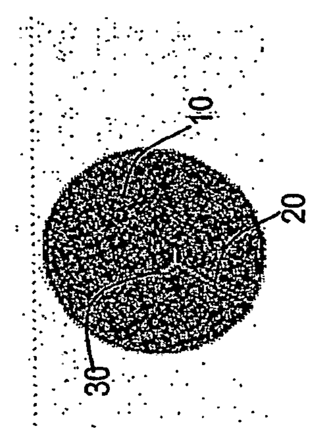

Figure 1

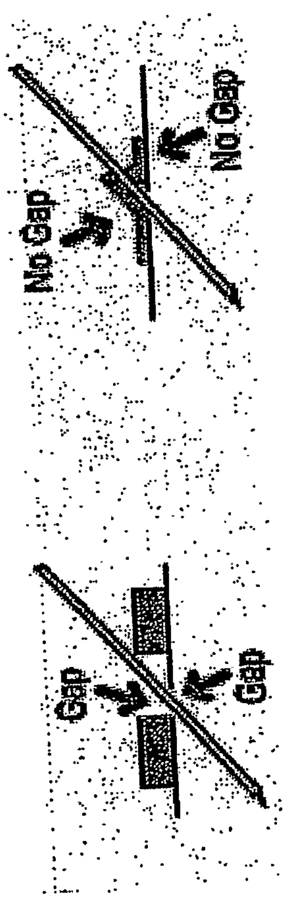

Figure 2